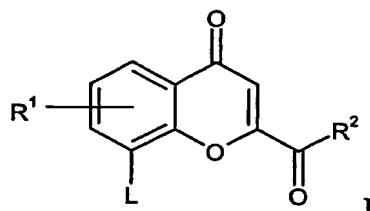


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FIELD OF INVENTION

The present invention provides a novel process for the preparation of chromone compounds having the general formula I:

5



wherein

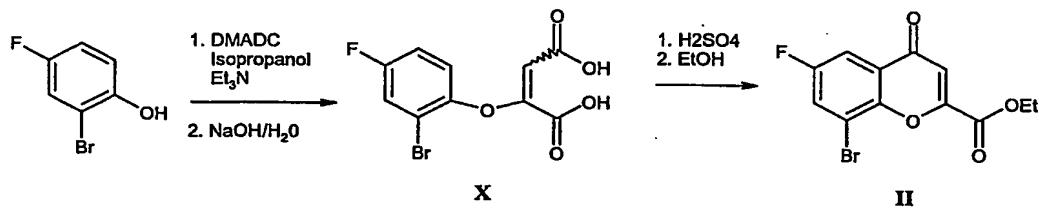
- R^1 is selected from H, C₁₋₁₀alkyl, halogen, amino, C₁₋₆alkyl-oxy, or hydroxy;
- L is a displaceable group selected from bromo, chloro, fluoro or iodo; and
- 10 R^2 is selected from H, C₁₋₆alkyl, halogen, hydroxy, amino, C₁₋₆alkyl-amino, C₁₋₆alkyl-carbonyl, C₁₋₆alkyl-oxy and C₁₋₆alkyl-oxycarbonyl optionally substituted by one or more groups selected from halogen, amino and hydroxy;

BACKGROUND OF THE INVENTION

15

The present invention relates to the preparation of chromone compounds that may be useful in the manufacture of potentially potent orally active 5-HT_{1B} receptor antagonist, useful in the treatment of depression, anxiety and other related diseases. An example of such a preparation is as follows:

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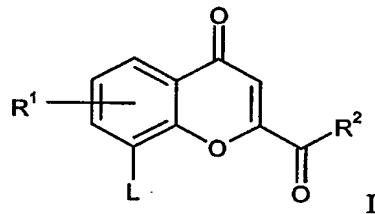
While this preparation leads to the chromone compound it also suffers from several drawbacks, making its viability for commercial production doubtful.

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Applicants provide a process for the preparation of chromone compounds of formula I that unexpectedly and surprisingly provide improvements in product yields, cost, energy consumption, reduction in the number of synthetic steps, improved scale up conditions, and
5 the like.

10 DESCRIPTION OF THE INVENTION

Provided herein is a process for preparing compounds of formula I:



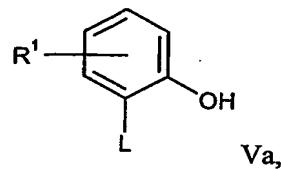
15 wherein

R¹ is selected from H, C₁₋₁₀alkyl, halogen, amino, C₁₋₆alkyl-oxy, or hydroxy;
L is a displaceable group selected from bromo, chloro, fluoro or iodo; and
R² is selected from H, C₁₋₆alkyl, halogen, hydroxy, amino, C₁₋₆alkyl-amino, C₁₋₆alkyl-
20 carbonyl, C₁₋₆alkyl-oxy and C₁₋₆alkyl-oxycarbonyl optionally substituted by one or more groups selected from halogen, amino and hydroxy;

comprising

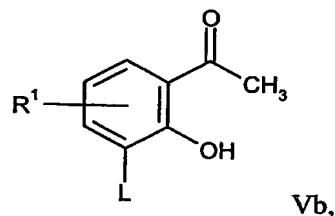
25 A) heating a mixture of a compound of formula Va:

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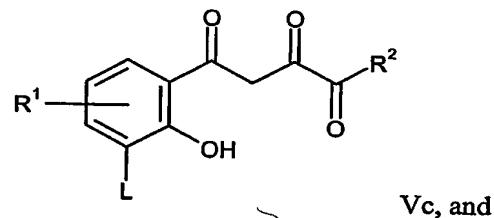
and an acetylating agent in the presence of a Lewis acid catalyst at a temperature and for a time effective to give compounds of formula Vb:

5



B) combining the compounds of formula Vb and a dicarbonyl compound to an alcohol solution at a temperature and for a time effective to give compounds of formula Vc:

10



C) heating the compound of formula Vc with a mixture of acids at a temperature and for a time effective to give compounds of formula I.

15

In another embodiment, R¹ is, independently, H, C₁-C₆ alkyl, halogen, hydroxyl, methoxy or cyano. In a more particular embodiment R¹ is, independently, hydrogen or fluoro.

20 In another embodiment, L is a displaceable group. In another embodiment L is a displaceable group selected from bromo, chloro, fluoro or iodo. In a more particular embodiment L is bromo.

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In another embodiment, R² is selected from H, C₁₋₆alkyl, halogen, hydroxy, amino or C₁₋₆alkyl-oxy optionally substituted by one or more groups selected from halogen, amino and hydroxy. In a more particular embodiment, R² is selected from H, C₁₋₆alkyl, C₁₋₆alkyl-oxy or hydroxy.

If necessary a number of different bases and solvents can be used for the above process. The above process may further include a step for separating, filtering or washing compounds that may be carried out in any number of ways known in the art.

10

In another embodiment, heating the compound of formula Va, the acetylating agent and the catalyst may be conducted at a temperature and for a time effective to provide compound Vb. In a more particular embodiment, the heating of formula Va, the acetylating agent and the catalyst may be conducted at a temperature between about 130 and about 135°C
15 for about 1 to 2 hours.

In another embodiment, the acetylating agent are those functional derivatives of carboxylic acids that contain an acyl group and that can undergo nucleophilic substitution. For example, suitable acetylating agents include acetic acid, acetic anhydride, acetamide, acetyl chloride, acetyl bromide and ethyl acetate. In a more particular embodiment, the acetylating agent may be acetyl chloride.

In another embodiment, the Lewis acid catalyst may be selected from aluminum chloride, zirconium tetrachloride, bromide tetrachloride, HF and phosphoric acid. In a more 25 particular embodiment, the Lewis acid catalyst may be selected from aluminum chloride or zirconium tetrachloride. In particular, the Lewis acid catalysts may be aluminum chloride.

In another embodiment the Lewis acid catalyst may be added in portions. In particular, the Lewis acid catalyst may be added in two portions.

30

In another embodiment, the pH level may be adjusted. In another embodiment, the pH level may be adjusted to about 7.

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In another embodiment, one of the carbonyl groups forming the dicarbonyl compound may be an ester. For example, suitable dicarbonyl compounds include Pyruvate or glyoxylate esters, methylglyoxal, and C₁₋₄oxalate. In particular, the dicarbonyl compound may be ethyl
5 oxalate.

In another embodiment, reacting the compound of formula Vb with a dicarbonyl compound in an alcohol solution may be conducted at a temperature and for a time effective to provide compound Vc. In a more particular embodiment, the reaction may be conducted at
10 a temperature between about 55 and about 60°C for a time between about 1 to 2 hours.

In another embodiment, the alcohol solution comprises sodium alkoxide in absolute alcohol. For example, suitable sodium alkoxides include sodium methoxide, sodium ethoxide sodium isopropoxide and sodium tert-butoxide. For example, suitable absolute alcohols
15 include methanol, ethanol, propanol, butanol, isobutanol and tert-butanol. In particular, the alcohol solution comprises sodium ethoxide in absolute ethanol.

In another embodiment, reacting the compound of formula Vc with a mixture of acid may be conducted at a temperature and for a time effective to provide compound I. In a more
20 particular embodiment, the reaction may be conducted at a temperature between about 70 and about 80°C for a time between about 1 to 2 hours.

In another embodiment, the mixture of acids may be a mixture of acetic and hydrochloric acid.
25

Minimizing the charge of aluminum chloride may help control any impurities that form during the above process.

Unless specified otherwise within this specification, the nomenclature used in this
30 specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is

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incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

5 The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms. Unless otherwise specified, "alkyl" generally includes both saturated alkyl and unsaturated alkyl.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

10 The term "aryl" used alone or as suffix or prefix, refers to a hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (e.g., $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, wherein the radical is located on a carbon of the aromatic ring.

15 The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more 20 double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

25 The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula -O-R, wherein -R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

30 Halogen includes fluorine, chlorine, bromine and iodine.

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When a first group, structure, or atom is "directly connected" to a second group, structure or atom, at least one atom of the first group, structure or atom forms a chemical bond with at least one atom of the second group, structure or atom.

- 5 "Saturated carbon" means a carbon atom in a structure, molecule or group wherein all the bonds connected to this carbon atom are single bond. In other words, there is no double or triple bonds connected to this carbon atom and this carbon atom generally adopts an sp^3 atomic orbital hybridization.
- 10 "Unsaturated carbon" means a carbon atom in a structure; molecule or group wherein at least one bond connected to this carbon atom is not a single bond. In other words, there is at least one double or triple bond connected to this carbon atom and this carbon atom generally adopts a sp or sp^2 atomic orbital hybridization.
- 15 The processes and synthetic methods described hereinthroughout may be carried out with or without a suitable solvent or base. Generally, suitable solvents are solvents which are substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e., temperatures which may range from the solvent's freezing temperature to the solvent's boiling temperature.
- 20 A given reaction may be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction, suitable solvents for a particular work-up following the reaction may be selected. For example, suitable solvents may include water, alcohols, hydrocarbon solvents and halogenated derivatives. In particular, water, dichloromethane, xylene, ethanol and methanol.
- 25

Examples

Preparation of 1-(3-bromo-5-fluoro-2-hydroxyphenyl)ethanone

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A mixture of 2-bromo-4-fluorophenol (64.0 kg, 1.00 mol equiv) and acetyl chloride (62.5 kg, 2.39 mol equiv) was stirred and heated at 50-55°C for one hour. Excess acetyl chloride (10.8 kg) was removed by distillation and the residue was cooled to 25-30°C then diluted with dichloromethane (120 L). The mixture was further cooled to 10-15°C and 5 aluminum chloride (51.0 kg, 1.15 mol equiv) was added in two portions. The temperature of the mixture was raised to 130-135°C over one hour during which time dichloromethane (80 L) was removed by distillation. The mixture was maintained at 130-135°C for one hour, diluted with xylene (250 L) and cooled to 10-15°C. The reaction mixture was added to a solution of 30% w/w hydrochloric acid (25 L) in water (500 L). The layers were separated 10 and the organic phase was extracted with 10% w/w sodium hydroxide solution (300 L). The aqueous extract was cooled to 10-15°C and adjusted to pH 6.8-7.2 with 30% w/w hydrochloric acid (55.0 kg). The solid was filtered off, washed with water (60 L), then with petroleum ether (100 L) and dried at 55-60°C under vacuum. The yield of 1-(3-bromo-5-fluoro-2-hydroxyphenyl)ethanone was 46.0 kg (60%).

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Preparation of ethyl 8-bromo-6-fluoro-4-oxo-4H-chromene-2-carboxylate

A mixture of 1-(3-bromo-5-fluoro-2-hydroxyphenyl)ethanone (46.0 kg, 1.00 mol equiv) and diethyl oxalate (172.0 kg, 6.00 mol equiv) was added to a solution of sodium 20 ethoxide (66.8 kg, 4.9 mol equiv) in absolute ethanol (250 L) at 60°C. The mixture was stirred at 55-60°C for one hour and ethanol was removed by distillation. The residual mixture was diluted with water (300 L) and the precipitated solid isolated by filtration. This solid was heated with a mixture of acetic acid (210 L) and 30 w/w hydrochloric acid (55.5 L) at 70-80°C for two hours. After cooling at 25°C, the mixture was diluted with water (150 L and 100 25 L), then with 12% w/w sodium bicarbonate solution (50 L) and finally methanol (100 L) before drying at 70°C under vacuum. The yield of ethyl 8-bromo-6-fluoro-4-oxo-4H-chromene-2-carboxylate was 38.6 kg (63%).